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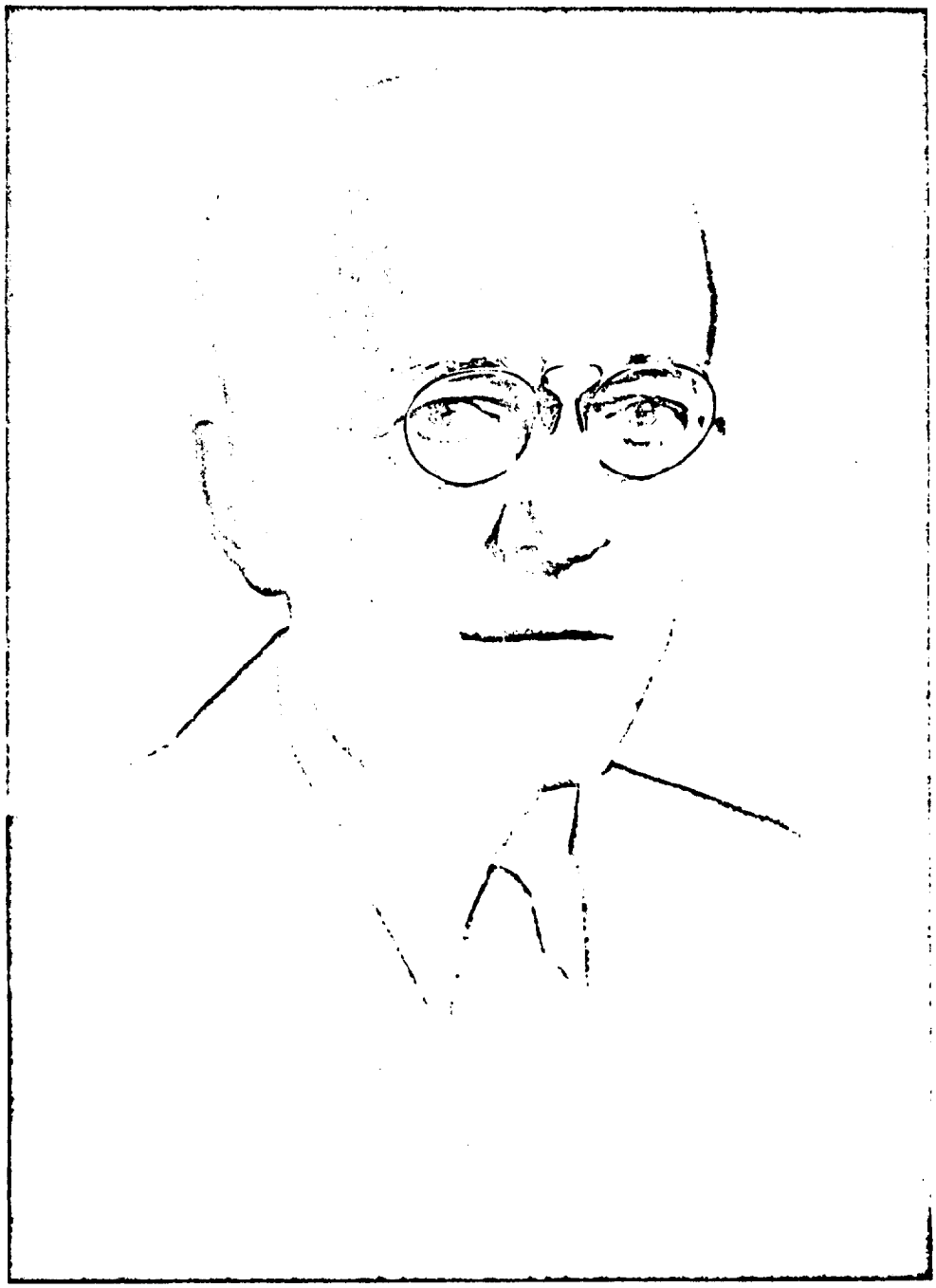

OSWALD THEODORE AVERY AND DNA

*ALVIN F. COBURN, M.D.**

To one who had no scientific association with Avery's work it seems appropriate to place the following information on the record. I am motivated to make this report because repeatedly I note that many persons in high echelons of science are unaware that Oswald T. Avery envisaged the implications of the discovery of his "transforming factor." As early as 1943 Avery did indeed understand the significance of DNA in microbial genetics, the discovery of which culminated his extraordinarily creative life as a member of the Rockefeller Institute.

Avery practiced meticulously the sermon that he often preached to his assistants and to the many younger colleagues who came to him for guidance: "Apply your brakes when tempted to blow your own horn." His rigorous self-discipline, along with constant modesty and a deep humility —in the noblest sense of the word—made it impossible for Avery to go far beyond the "facts" in his published work. His high regard for the printed word deterred him from theorizing in print—only the "facts" were admissible—and his own wisdom certainly prevented him from pointing out the great significance of his discoveries, perhaps even to the many young men who had the great good fortune to work with "the Fess" (short for professor), as he was called.

Prior to 1940 O. T. Avery was only a name—a name which belonged with Theobald Smith, F. Gowland Hopkins, and Marie Curie, persons who had created new disciplines for mankind to explore. Avery had opened the doors to the world of immunochemistry, an achievement vividly brought home by Michael Heidelberger, who occupied the laboratory contiguous to mine. Whenever Fess Avery was mentioned, Heidelberger manifested reverence to such a degree that there was a distinct pause

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in the conversation. For Heidelberger and the many younger scientists who had sought out Avery for advice on their research, the Fess was considered the mentor par excellence. It was well known that Avery examined every facet of a problem so thoroughly that the "consultation" rarely lasted less than two hours, and the research problem was frequently explored in depth for three to five hours. However, the Fess maintained a silence on his own work.

This creative and sympathetic interest in the research of others touched me personally in April 1942. Because I was ignorant of Avery's studies in progress, our first meeting was exceedingly painful to me. I had just been called on active duty by the U.S. Navy and was invited to attend an April meeting of the National Research Council in Washington, D.C. The subject to be discussed was streptococcal problems in the armed services, for already the navy was confronted with a high incidence of rheumatic fever in the recruit training camps at the Great Lakes Training Center. More than a dozen distinguished civilian biologists were assembled in the conference room. There were tedious harangues about the streptococcal menace. Each speaker seemed to concentrate on the periphery but declined to take an aggressive stance.

Finally, I was questioned. Nervously, I stated that without adequate preventive medicine or control measures, three things could reasonably be expected to happen: (1) There would be a high incidence and rapid spread of hemolytic streptococcal respiratory infections. (2) Certain strains would develop "mutants" or "sports" that would be highly infective (as contagious as postinfluenzal streptococcal pneumonia in World War I at army camps in Texas). (3) Perhaps one or more of the streptococcal mutants would be genetically resistant to sulfonamides.

There was dead silence when I had finished. Nobody spoke a word of agreement or approval; there seemed to be no interest in what was obviously a figment of my imagination. Presumably I had used words that were not acceptable in scientific circles—*genetic changes, bacterial variation, mutants, sports.*

Soon it was time to recess, and we paraded to the lower level for a standup snack lunch. Chagrined, depressed, and fearful of reprimand for my shocking verbal goof, I picked up a sandwich and a bottle of Coca Cola and slunk into a far corner to recover from my embarassment. Then, although I had thought that not one person at our conference table had

believed a single word I had uttered, a short man with a soft voice joined me and said, "I was most interested in your remarks. Please tell me more." Thus, O. T. Avery, in his gentle way, opened my flood gates, and I expressed my concern to him in detail.

As I documented these statements with findings from our laboratory and referred to the recent report of Beadle and Tatum [1], Avery's attention increased. It had not occurred to me that the Fess had any interest in bacterial variation; so I was surprised when he invited me to join him for supper on the train back to New York. I well remember that during the course of our dinner conversation he emphasized how much he wished he were my age so as to be able to work on some of the biological problems that fascinated me. At that time, I knew only that Avery was *sympatico* with the young naval officer who believed that changes in the genes of beta hemolytic streptococcus might result in different biochemical mechanisms and increased infectivity for man.

One year passed. It was March 1943. Hemolytic streptococcal infections had become the navy's greatest stateside medical problem, and the beds of the hospital at the Rockefeller Institute were filled with the navy's enlisted men from New York's pier number 92. Practically all of these patients were infected with a single serological type, group A hemolytic streptococcus (type 19). Avery's sympathetic understanding back in 1942 had not been misplaced, and I felt that it would not be too much of a liberty for me to express my appreciation by inviting the Fess to spend a Sunday with us before the navy transferred me to Portsmouth, Virginia.

I met Avery at the North White Plains Station and drove him home. He suggested that we take a walk. I looked at his highly polished black shoes and his neatly pressed blue Sunday suit and hesitated. Nevertheless, he wanted to walk; so we set out for a two-hour hike through Conyer's orchard and the Round Hill Road back to our home. Except for this particular day the Fess always wanted to listen prior to expressing his opinion and before generously offering sound advice. However, on that March Sunday the dialogue was different; Avery wanted to talk; for once he was exuberant!

He said, "You are going away; I do not know when we shall meet again; I want to give you a little information that some day may be helpful to you in your work." For the only time in our many dialogues I had no idea what was on Avery's mind. He said that on the preceding day he

had reported at a meeting of the trustees of the Rockefeller Institute his work on the "transforming factor." I was still completely in the dark until he described work done fifteen years previously by Fred Griffith of London. At last, I began to tune in on Avery's wavelength; Griffith's name and work were familiar to me.

It so happened that in 1931 Fred Griffith had extended to me a helping hand across the Atlantic Ocean in the serological identification of *Streptococcus pyogenes*. But Avery, I knew, was dedicated to the pneumococcus! What was the connection between these two bacteriologists? For two hours the Fess related his story, beginning with Griffith's 1928 publication on the changing of the serologic type of the pneumococcus, which sparked Avery's own research, and concluding with his report of the day before to his board of trustees on the chemistry of "the transforming factor."

Then came the climactic remark: the factor which transformed the genetically transmitted type of the pneumococcus was desoxyribonucleic acid! My first reaction, *not* expressed aloud, was: "So what? How is this going to help us win the war?" All that I could then do was to thank the Fess perfunctorily for telling me his most intimate secret. My thoughts were wandering to triumphant Rommel in North Africa and the Japanese fleet around the Coral Sea. Nevertheless, the fact that Avery had taken the trouble to brief me on a factor in genetic control of the pneumococcus had made its impression.

The incubation period for understanding the implication of the information that Avery had given me was approximately eight weeks (rather long for an infecting agent!). By mid-May I was living in a room in Virginia with windows blacked out at night, only yards away from the waves of the Atlantic Ocean. Weekly, German submarines were sinking oil tankers only a few miles off shore. The war prospects looked as black as the beach did on the morning after an oil tanker was sunk. My thoughts sought an escape from the grim reality ahead. It was under these circumstances that I recalled what the Fess had told me as a gift for any future association with streptococcal problems.

Then flashed through my mind this idea: perhaps this desoxyribonucleic acid will not only change bacteria but will also modify Charles L. Hoagland's culture of vaccinia virus. Perhaps it will change the genetically controlled biochemical mechanisms of all microorganisms! The excite-

ment within me was so great that I immediately wrote the Fess. Two things had suddenly become as clear as crystal: first, Avery, through his decades of dedication to the study of the pneumococcus, had at long last in his hands a substance of enormous importance to microbial activity; second, I realized for the first time how deeply Avery's work was founded on the discovery made by Fred Griffith. It therefore seemed appropriate to send to Avery my picture of Griffith. Avery treasured this 1936 snapshot of the English bacteriologist with his dog, Bobby, which it has been said was the only existing picture of F. Griffith.

Two years later, in January 1946, returning "stateside" after World War II, I revisited the Rockefeller Institute and lunched with Dr. Charles Hoagland. I asked casually, "What's new in science since I left these shores?" He responded immediately. He did not mention his own important work or the work of his colleagues at the institute.

"The geneticists," he replied, "have caught on with enthusiasm to the significance of the Fess's discovery of desoxyribonucleic acid and are very excited about it." It was only then, through the catalyzing mind of Charles Hoagland, that I realized for the first time that the Fess had produced information that transcended the microbial world and might even be involved in the genetic problems of mankind. Avery had probably envisaged this when he "lectured" to me in March 1943. But always, as in the past, Avery kept his foot on the brakes and gave me only the facts which might be relevant to my own microbial research interests.

During the next decade (both in New York and in Nashville) Avery expressed to me his interests in the pursuit of certain studies with the collaboration of a geneticist. Later he explained why he preferred to leave the next step to others. This decision he had made prior to that crisp fall morning in 1952 when Dr. Roy C. Avery brought in the morning newspaper. The front page proclaimed that the Nobel Prize had been given for the discovery of streptomycin. O. T. Avery seemed pleased that an American bacteriologist was the recipient.

Recently, after the passing of nearly a quarter century, I received an inquiry from one of America's most distinguished geneticists, a member of the coterie of Nobel laureates spawned by Avery's identification of his transforming factor. The question posed was: Did Avery ever understand the implications to genetics of his own discovery of DNA? The answer was

obviously "yes." Had the brilliant geneticist been confounded by Avery's modesty?

I replied that I knew from a conversation which I had held with O. T. Avery in 1943 that he was certainly aware at that early time of the significance of his transforming factor for microbial genetics, and probably also of its implications for human genetics. In any case, Avery was certainly aware of the broad implications for mankind before 1946, since by then the geneticists were expressing keen interest in his work on desoxyribonucleic acid. I only wished in replying to the inquiry that there were some way of documenting the substance of the conversation that Avery and I had had in March 1943. There were no letters; Avery budgeted his correspondence! He wrote to his family, and he was meticulously careful to send "bread and butter" thank-you notes, which his hostesses found to be masterpieces of gallantry. Until 1969 I was unaware that he had written anyone concerning the implications of his great discovery. It was logical to assume that my letter of May 1943 to the Fess, in which I recalled our March conversation, had no doubt long since been destroyed. At least this is what I presumed years after O. T. Avery's death.

Fortuitously I wrote to the Fess's brother, Dr. Roy C. Avery, in Nashville and made a personal request. Could I have back the only available snapshot of Fred Griffith sent to the Fess in May 1943, the picture that he had framed and always kept on his desk? I heard nothing for months and concluded that the picture had been thrown away. In due course, however, Dr. Avery located the picture cached in a trunk. When the frame was removed for mailing, he found that an extraneous object had been placed as a backing for the picture—my letter of May 25, 1943 to the Fess, which revealed my excitement upon catching on to the significance of what Fess had told me that March Sunday morning in 1943!

To document this narrative I submit: (1) A snapshot of O. T. Avery taken after dinner on a Sunday in March 1943, the day after he had announced informally to his board of trustees that he had discovered that his "transforming factor" was desoxyribonucleic acid. (2) My letter to Avery in 1943, found nearly a quarter century later incarcerated by the Fess in the frame of the picture of his peer Fred Griffith of the British Ministry of Health, a rare biologist whom he had never met but to whom he must have always felt indebted.

Since drafting this exposition I have been informed that the substance of

FIG. 1.—O. T. Avery with a young Coburn, at our home March 1943

NORFOLK NAVAL HOSPITAL
PORTSMOUTH, VIRGINIA

Tuesday night
5.25.43

Dear Rene,

Now that a month has slipped by since you were kind enough to join us and treat the children, young and old, with those delicious sherry chocolates. To one member of the Colvin family you have a much greater debt, one that will always be remembered. Hearing from you the evolution of your great work from 1925 to 1943 with the rare spirit harvested at the end was the most inspiring experience that I have had in medicine. Out of it all came one deep conviction—it is up to the Free to pursue such important studies until the war is over and some of us become available to help him carry on.

Also it seemed to me that you left the close association of your work with that of Griffith. I'd add that you two never met in there was much in common. And I know what great satisfaction would be Griffith's if he could know what you have done. Because of this it seemed only fit that Griffith picture should be near your work. So now that our little picture of Mrs. Griffith and Wally on the Downs near Brighton is the only one in existence. Alice is mailing it to you with our affection.

Fig. 2—Reproduction of my letter to Avery, May 26, 1943

Avery's March 1943 revelation to me was recorded in a letter of May 13, 1943 to his brother, Roy C. Avery. This was published in part in 1964 by Carsten Bresch [2, p. 130] as follows:

Die molekulare Grundlage der genetischen Information Avery beschrieb am 13.5.1943 diese Entdeckung—wohl die grosste der Genetik seit MENDEL—in einem Brief an seinen Bruder:[1] "... But at last perhaps we have it. The active substance is not digested by crystalline trypsin or chymotrypsin, it does not lose activity when treated with crystalline ribonuclease ... polysaccharide can be removed.... Lipids can be extracted ... without impairing biological activity. The extract can be deproteinized.... When extracts, treated and purified to this extent ... are further fractionated by the dropwise addition of absolute ethyl alcohol an interesting thing occurs. When alcohol reaches a concentration of about 9/10 volume there separates out a fibrous substance which on stirring the mixture wraps itself about the glass rod like thread on a spool.... The fibrous material is ... highly reactive and on elementary analysis conforms very closely to the theoretical values of pure desoxyribose nucleic acid (thymus type). (Who could have guessed it) ... depolymerase capable of breaking down known authentic samples of desoxyribose nucleic acid has been found to destroy the activity of our substance—indirect evidence but suggestive that the transforming principle as isolated may belong to this class of chemical substance.... If we are right, and of course that is not yet proven, then it means that nucleic acids are not merely structurally important but functionally active substances in determining the biochemical activities and specific characteristics of cells.... But today it takes a lot of well documented evidence to convince anyone that the sodium salt of desoxyribose nucleic acid, protein free, could possibly be endowed with such biologically active and specific properties and that is the evidence we are now trying to get. It is lots of fun to blow bubbles but it is wiser to prick them yourself before someone else tries to."

[1] Original im Besitz von R. C. Avery, Vanderbilt University, Nashville, Tenn.

On November 1, 1943 Avery, McLeod, and McCarty submitted for publication their epic discovery [3]. In this report they cite as the origin of their work the findings of F. Griffith [4].

In conclusion, in March 1943 when concerned with streptococcal epidemics [5], I learned that the serologic type of the pneumococcus could be transformed by desoxyribonucleic acid. And so it came to pass: singleness of purpose, continuity of work, a laboratory haven protected by the constant vigilance of Rufus Cole, this summation at long last bore a rare fruit. Avery's devotion to the biology and chemistry of one bacterium over the decades produced a discovery—"wohl die grosste in der Genetik seit Mendel" [2]. It was the immunochemist O. T. Avery who, while making the most significant contribution to modern genetics, ushered in a new era for the human family. Although Avery may not have used the term *DNA*, he was certainly the first to demonstrate its role in bacterial genetics, and he was one of the first, if not the first, to envision its signifi-

cance for all mankind. As a man of great wisdom he made no claims, and the enormous significance of his contribution to the future of science was overlooked by most of his distinguished peers.

I share the reverence held by many for the selflessness and conservatism that characterized the Fess and wish that I could have presented this personal information anonymously, but there seemed no alternative to telling this story in the first person. In fact, I shall complete this exposition by citing an example of Avery's high degree of cautiousness as told me by Dr. Yale Kneeland of the Columbia-Presbyterian Medical Center. This occurred during a drive from Manhattan to Long Island across the windswept Triborough Bridge. Dr. Kneeland was at the wheel beside his passenger, Avery, who looked down at the dashboard and saw the indicator at the number 80. Avery inquired: "Don't you think that we are travelling a bit too fast, Dr. Kneeland?" The latter then also looked down, saw what was upsetting the ever-cautious Fess, and replied: "Dr. Avery, according to the speedometer we are going a bit less than 40 miles an hour. That's the radio indicator that you are looking at!"

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LOGIC

A professor of symbolic logic
Grew irked by his task pedagogic.
He exclaimed to his class,
"Everyone is an ass,
And your logic is all zoologic!"

Joel H. Hildebrand